July 24, 1973

Carl Djerassi
Department of Chemistry

Joshua Lederberg
Department of Genetics

Viruses in insect control

Dear Carl,

I have a number of comments which I will just give to you in rough form without taking time to organize them in more detail. Generally speaking I think that the regulatory approach to this is as short-sighted as was the idea that the IUD was going to be the panacea without side-effects.

The most critical basic problem is to know exactly what happens to virus DNA when it enters the mammal. It is not enough to say that we are unable to detect the propagation of the virus since the same could be said for many tumor viruses until we develop special techniques. Until there is affirmative evidence about the manner in which such virus DNA is disposed of, the matter should be regarded as absolutely unsettled. This concept is, of course, also relevant to the unduly complacent attitude which is taken, page 9, with respect to avoiding long-term and reproduction studies. Even apart from the question whether the virus DNA itself persists in some form, there is no logical a priori argument against the possibility of triggering a chain of events that may not appear for many years after initial exposure. I do not believe that insect viruses would prove to be similar to DES but one could have made the same statement about that, namely that it is "neither toxic nor capable of multiplication or long persistence in vertebrate systems".

I turn now to passing comments on the text. Besides persistence in vertebrates questions should be asked about the survival of insect viruses in mosquitos and other arthropods that traditionally have been important as vectors of virus disease for man. Conversely, one of the strongest arguments for the safety of insect viruses is their already extensive natural prevalence, but this is an argument that as powerful as it is must be scrutinized very carefully. In particular, we must be sure that the actual biological status of the virus as used in agricultural practice is acceptably comparable to that of its occurrence in nature. There is, of course, a logical contradiction since if this identity were complete there would be no need to provide the virus by artificial spread.

I am rather alarmed by rather passing remarks about "intrinsic contamination" of virus preparations when the biological purity of the operational material is a matter of utmost concern.

The logic of the recommended dosages for testing escapes me. On the one hand, the requirement to test amounts to be distributed over 100 acres seems unduly demanding; on the other hand, to apply the criterion of a dose level per kilogram of animal is a way of evading the question of toxicity. If there is an effective particle in such a preparation or if there are

biological effects that result from infectivity, it is not going to make very much difference whether that particle is injected into a 25 gram mouse or a 100 kilogram man.

Particular attention should be given to studies of the potential interaction of insect viruses with other pathogens and under the general heading of immuno-deficient hosts they should be tested by inoculation into thymectomized animals and newborns by analogy with well-known studies on tumor viruses.

It is also important that we understand the potential evolution of insect viruses much better before we embark on their large-scale introduction into the environment.

Page 9, the Guinea pig is an excellent animal to discover respiratory sensitization but since so many substances can induce this in Guinea pigs without their necessarily being of clinical consequence to man, we will have to devise more realistic protocols on this point.

I would appreciate your letting me know whether this material has in fact appeared in the federal register as I may be interested in filing a formal comment as previewed on page 12.